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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,729	DARTEIL ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7,10 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,10 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Claims 1-3, 5, 7, 10, and 15-22 are considered in this action. Claims 4, 6, 8-9, 11-14, and 23-33 have been cancelled.

Response to Applicant's Arguments in Response to Restriction

Applicant's election with traverse of Group IV, Claims 1-23, 25-27, 29, and 31, drawn to a nucleic acid encoding a modified PPARγ in the paper dated and received September 26, 2003, is acknowledged. The traversal is on the ground(s) that all of the claims share a special technical feature. This is not found persuasive because the claimed inventions are drawn to compositions that have been recognized in the art to have different structures and functions, therefore they lack the same special technical feature (WO 98/21349). Moreover, Applicant's specification specifically admits that the PPARs belong to three distinct groups (p. 16).

Applicant's traverse on the grounds that the Office has improperly limited the scope of the claims through the Restriction Requirement, e.g., limiting the scope of Claim 1 to specific species recited in the specification and certain dependent claims. This is not considered persuasive because, while they are species, they have different structure and function, therefore, they are different inventions and not just species.

Applicants further point out that Claim 30 was not addressed in the Restriction Requirement. Examiner admits that this claim was missed. Claim 30 would properly have been included in Groups III, IV, VII, VIII, XI, XII, XV, and XVI of the Restriction Requirement; however, because this claim has been cancelled, the assignment of this claim is considered moot.

Applicants traverse on the grounds that a thorough search and examination of the claims of Group IV would necessarily encompass a search and examination of the claims of Groups VIII and XII, and that therefore a serious additional burden is not placed on the Examiner, also quoting MPEP § 803 for the statement that "if the search and examination of the entire application can be made without serious burden, the examiner must examine it on the merits". This is not considered persuasive because, while there would have been a search burden, as the steps of the methods are different and not interchangeable, the burden is not only of search, but of examination.

Applicants respectfully submit that the office should rejoin Groups XVI and XVIII, should one or more product claims be found allowable. These groups will not be rejoined because they encompass different ligands of different structure and function, and therefore, the method steps of one would not necessarily work in the method of the other; however, this argument is also considered moot in view of the cancellation of those claims.

The requirement is still deemed proper and is therefore made FINAL.

With regard to the currently-amended claims, because the claims retain recitations of "a PPAR", those recitations will only considered with regard modified forms of PPARγ, where those references are not to PPAR response elements. Moreover, any PPAR, other than modified forms of PPARγ, will not be considered.

Claim Objections

Claims 1-3, 5, 7, 10, and 15-22 are objected-to for comprising non-elected subject matter. In the restriction, as stated above, Applicant's elected "modified PPARγ" as the invention to be examined. Each of these claims are drawn to "a PPAR", except Claim 15, which specifically states "a PPARα or a PPARγ". None of these claims is drawn to the scope of the elected restriction: a modified PPARγ. Applicants are required to amend the claims to reflect the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 states the limitation "a modified PPAR". It is unclear what the metes and bounds of "a modified PPAR" comprises.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7, 10, and 15-22 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5, 7, 10, and 15-22 encompass any modified PPARγ, which encompasses any mutation to PPARγ. Some Claims, notably Claim 16, requires further mutations wild-type PPARγ, but such Claims comprise the mutation specifically recited. Therefore, these Claims encompass not only the mutation recited, but any other modification of PPARγ.

However, the specification broadly discloses that such modifications would be defined because they are functional variants (pp. 10-12). In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, two multi-ligand binding domain comprising PPARγ proteins have been disclosed (examples), and only broad disclosure is given with respect to other species (pp. 10-12). The specification does not provide any disclosure as to what would have been the required structure to determine the differences between the various species of the genus. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, i.e., other than sequence, specific features and functional attributes that would distinguidsh different members of the claimed genus. In the instant case, the only identifying characteristic is its functional behavior.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), which states:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309), 97 F.2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not, however, fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any mutant PPARγ beyond those consisting of multiple ligand-binding sites. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claims 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a modified PPARγ, wherein the modification is the addition of a second ligand-binding domain to wild-type PPARγ and vectors encoding such nucleic acids, does not reasonably provide enablement for nucleic acids encoding modified PPARγ proteins containing more than two ligand-binding domains or vectors comprising such

nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Background

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

The Breadth of the Claims

Claims 16 is broad in scope. Claim 16 encompasses any composition comprising (1) any nucleic acid of interest under the control of any inducible promoter comprising at least one of any PPAR response element and any minimal transcriptional promoter, (2) a nucleic acid encoding any modified PPARγ with more than one ligand binding site, under the control of any transcriptional promoter. It is noted that the full breadth of Claim 16 encompasses all the elements of Claim 1 or Claim 2.

What the scope of enablement is directed to is the number of ligand binding sites, and that is what Examiner will direct his analysis to. Claim 16, with respect to the number of ligand binding sites is broad, because it encompasses the inclusion of any number (more than one) of ligand binding sites.

The Nature of the Invention

The invention is in the nature of modified proteins. Such modifications of proteins are not generally predictable in the art.

With regard to the modification of proteins, Benkovic, et al (2003) Science, 301: 1196-1202 provides a sufficient perspective. Benkovic is only able to review proffered hypotheses, supportive and occasionally counterintuitive experiments and our current understanding or ignorance (Introduction). Moreover, Benkovic makes clear that while some progress has been made, there is much more to be determined, and this is at the level of minor structural, not at the level of the large concatamers modifying a protein, as encompassed by the Claim (Article in general).

In reviewing Benkovic, it is clear that one of skill in the art would require, in order to make and/or use a new invention in the field, a showing that the number of multiple-ligand binding domains would not destroy the folding of the protein to such an extent that the function of the protein is removed.

The State of the Art

Benkovic demonstrates that the art is counterintuitive and no single coherent theory is present to predict whether any single mutation, much less large contatameric domain perturbations, would produce a beneficial or negative effect on a protein's function.

Moreover, there is no art of record demonstrating any PPAR with more than one ligand-binding domain.

Hence, absent a reasonable showing in the disclosure by Applicant, Claim 16 would not be enabled for any multi-ligand-binding-domain comprising PPARγ.

The Level of One of Ordinary Skill in the Art

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Level of Predictability in the Art

Because at least Benkovic demonstrates that the art for protein modification is not predictable, even for small perturbations, much less the larger perturbations encompassed by Applicants Claim, the skilled Artisan at the time of invention by Applicant could not predict, in

the absence of proof to the contrary, that such multi-ligand-binding-domain comprising PPARγ would fold properly and be able to function.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for multi-ligand-comprising PPARγs.

The Amount of Direction and Guidance provided by Applicant

The specification broadly discusses the compositions of the invention, and further discusses that the PPARs may contain many ligand binding sites, particularly 2 ligand binding sites (pp. 17-19).

Outside of the broad discussion by applicant, and specific discussion of one PPAR containing 2 ligand-binding sites (p. 18), there is a lack of guidance and direction as to how these multiple ligand binding domains are to be incorporated into the PPAR.

Because of the lack of direction and guidance that would allow one of skill in the art to reasonably predict that such proteins would fold and function properly, the examples would be required to provide a very strong showing of effectiveness. Absent this strong showing, it would have required undue experimentation to make the invention within its full scope.

The Existence of Working Examples

Example 1 demonstrates the assembly of promoters that are inducible by PPARs. Example 2 demonstrates the specificity of PPARs for different promoters. Example 3 demonstrates some more promoters inducible by PPARs. Example 5 demonstrates the construction of PPARγ with 1 or 2 ligand-binding domains. Example 6 demonstrates increases in the final activity of inducible promoters due to response elements. Example 7 demonstrates

construction of the compositions containing genes driven by inducible promoters and nucleic acids encoding PPARs. Examples 8 and 9 demonstrate that PPARγs with one or two ligand binding domains induce transcription from PPAR response elements *in vitro*. Examples 10-14 demonstrate *in vivo* induction of transcription, the use of various genes, and the use of various ligands.

While Applicant has shown PPARγs with one or two ligand-binding-domains, and that such PPARs induce transcription from PPAR response elements, Applicants have not shown that more than two ligand binding domains will similarly fold and induce transcription from such PPAR response elements.

The Quantity of Exprimentation Needed to Make and/or Use the Invention

Because of the lack of enough working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention within the full scope as claimed by applicant.

Conclusion

Because of the large of experimentation required to make and/or use the invention within the full scope of each claim, as claimed by applicant, such experimentation is considered undue, and therefore, Claim 16 is not enabled for more than two ligand-binding domains within the PPARγ.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 10, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mukherjee, et al. (1997) J. Biol. Chem., 272(12): 8071-76.

With regard to Claim 1-3, 7, 10, 15, and 17, Mukherjee teaches a composition for cotransfection assays comprising a first nucleic acid encoding a protein of interest under the control of a minimal promoter and a at least one PPAR response element (pPPREA3-tk-Luc, Figs. 4 & 5, Experimental Procedures). Moreover Mukerjee teaches a second nucleic acid of interest comprising PPARγ under the control of a transcriptional promoter (pCMVhPPARγ2 or pCMVhPPARγ1, Figs. 4 & 5, Experimental Procedures). Furthermore, Mukherjee teaches an additional construct comprising a nucleic acid sequence encoding RXR under the control of a transcriptional promoter(Figure 5, pRXmRXRβ). Also, each of these constructs are on plasmids (Figure 5). Still also, Mukherjee teaches the addition of a ligand for a PPAR (Figure 5, BRL 49653 and LG 268).

Mukherjee, however, teaches 2 PPARγ proteins, and PPARγ1 may be considered to be a modified PPARγ2. Also, Mukherjee teaches Thiazolidinediones and RXRs appear to act as

activators of PPARγ (Discussion in general; Introduction in general; Figure 5), and that it would be useful to dissect PPARγ action (Introduction). Moreover, in the discussion, Mukherjee makes it clear that is unknown how thiazolidinediones activate PPARs.

Because of the teachings of Mukherjee, it would have been obvious to modify the PPARγ genes of Mukherjee in order to dissect PPARγ action (Introduction). Moreover, one would have been motivated to do so in order to map the activation domain of PPARγ that responds to thiazolidinediones or RXRs. Lastly, one of skill in the art would have had a reasonable expectation of success because the cotransfection assay was shown to be successful in Mukherjee.

Claims 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mukherjee as applied to claim 1 above, and further in view of U.S. Patent No. 5,814,618 to Bujard, et al.

With regard to Claims 18-22, Mukherjee teaches a composition for cotransfection assays comprising a first nucleic acid encoding a protein of interest under the control of a minimal promoter and a at least one PPAR response element (pPPREA3-tk-Luc, Figs. 4 & 5, Experimental Procedures). Moreover Mukerjee teaches a second nucleic acid of interest comprising PPARγ under the control of a transcriptional promoter (pCMVhPPARγ2 or pCMVhPPARγ1, Figs. 4 & 5, Experimental Procedures). Mukherjee, also teaches 2 PPARγ proteins, and PPARγ1 may be considered to be a modified PPARγ2. Also, Mukherjee teaches Thiazolidinediones and RXRs appear to act as activators of PPARγ (Discussion in general; Introduction in general; Figure 5), and that it would be useful to dissect PPARγ action

(Introduction). Moreover, in the discussion, Mukherjee makes it clear that is unknown how thiazolidinediones activate PPARs.

However, Mukherjee does not teach one vector comprising the nucleic acid of interest under control of a minimal promoter and a at least 1 PPAR response element and the second nucleic acid of interest encoding a PPARγ under the control of a transcriptional promoter.

On the other hand, Bujard teaches methods of regulating gene expression with tetracycline using compositions comprising a nucleic acid of interest under control of a promoter and a tetracycline-responsive region, and a second nucleic acid sequence of interest comprising a tetracycline-derived chimera that induces transcription (col. 19). Furthermore, Bujard teaches that these sequences may be in one vector (cols. 11-13). Moreover, the system may be used for coordinate regulation of two nucleotide sequences linked to the same tet-operator (col. 20; col. 22), and may form bi-directional transcription from one operator (col. 20). Lastly, Bujard teaches that such vectors may control multiple nucleotide sequences, and they may be regulated by such inducible or repressible promoters (col. 22).

Therefore, it would have been obvious for one of skill in the art to modify the vectors of Mukherjee to form one single vector, wherein the coding regions were under the control of the same inducible promoter, whether bi-directional or unidirectional. One would have been motivated to do so in order to control the relative amounts of nucleic acid encoding PPAR to that encoding reporter, in to order to provide a higher level of control in the dissection experiments, because, if one group had higher levels of vector encoding PPAR compared to another, higher levels of PPAR activation would be expected and such would obscure the data when dissecting such PPAR activity. Moreover, one would have had a reasonable expectation of success because

the vector of Mukherjee had already been shown effective, and Bujard demonstrates that such single-vector systems are possible.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (703) 305-4460 and will be (571) 272-0729 after 12 January 2004. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051 and will be (571) 272-0734 after 12 January 2004. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER